

CLAIMS

What is claimed:

1. A method of treating or preventing a coronary disorder in a subject comprising
5 administering a therapeutically effective amount of a TNF α antibody, or an antigen-binding fragment thereof, to the subject, wherein the antibody dissociates from human TNF α with a K_d of 1×10^{-8} M or less and a K_{off} rate constant of 1×10^{-3} s $^{-1}$ or less, both determined by surface plasmon resonance, and neutralizes human TNF α cytotoxicity in a standard *in vitro* L929 assay with an IC $_{50}$ of 1×10^{-7} M or less, such
10 that the coronary disorder is treated or prevented.
2. A method of treating or preventing a coronary disorder in a subject comprising administering a therapeutically effective amount a TNF α antibody, or an antigen-binding fragment thereof, with the following characteristics:
 - 15 a) dissociates from human TNF α with a K_{off} rate constant of 1×10^{-3} s $^{-1}$ or less, as determined by surface plasmon resonance;
 - b) has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, or modified from SEQ ID NO: 3 by a single alanine substitution at position 1, 4, 5, 7 or 8 or by one to five conservative amino acid substitutions at positions 1, 3, 4, 6,
20 7, 8 and/or 9;
 - c) has a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12, such that said coronary disorder is treated
25 or prevented.
3. A method of treating or preventing a coronary disorder in a subject comprising administering a therapeutically effective amount a TNF α antibody, or an antigen-binding fragment thereof, with a light chain variable region (LCVR) comprising the amino acid
30 sequence of SEQ ID NO: 1 and a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 2, such that said coronary disorder is treated or prevented.

4. The method of any one of claims 1, 2, and 3, wherein the antibody, or antigen-binding fragment thereof, is D2E7.
5. The method of any one of claims 1, 2, and 3, wherein the coronary disorder is restenosis.
6. The method of any one of claims 1, 2, and 3, wherein the coronary disorder is selected from the group consisting of acute congestive heart failure, an acute coronary syndrome (including angina and myocardial infarction), arterosclerosis, chronic arterosclerosis, cardiomyopathy, congestive heart failure (chronic and acute), and rheumatic heart disease.
7. A method of treating or preventing restenosis in a subject comprising administering a therapeutically effective amount of a TNF α antibody, or an antigen-binding fragment thereof, to the subject, wherein the antibody dissociates from human TNF α with a K_d of 1×10^{-8} M or less and a K_{off} rate constant of 1×10^{-3} s $^{-1}$ or less, both determined by surface plasmon resonance, and neutralizes human TNF α cytotoxicity in a standard *in vitro* L929 assay with an IC $_{50}$ of 1×10^{-7} M or less, such that said restenosis is treated or prevented.
8. A method of treating or preventing restenosis in a subject comprising administering a therapeutically effective amount a TNF α antibody, or an antigen-binding fragment thereof, with the following characteristics:
- a) dissociates from human TNF α with a K_{off} rate constant of 1×10^{-3} s $^{-1}$ or less, as determined by surface plasmon resonance;
- b) has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, or modified from SEQ ID NO: 3 by a single alanine substitution at position 1, 4, 5, 7 or 8 or by one to five conservative amino acid substitutions at positions 1, 3, 4, 6, 7, 8 and/or 9;
- c) has a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2,

3, 4, 5, 6, 8, 9, 10 or 11 or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12, such that said restenosis is treated or prevented.

- 5 9. A method of treating or preventing restenosis in a subject comprising administering a therapeutically effective amount a TNF α antibody, or an antigen-binding fragment thereof, with a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 2, such that said restenosis is treated or prevented.

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10. The method of any one of claims 7, 8, or 9, wherein the TNF α antibody, or antigen binding fragment thereof, is D2E7.

11. The method of any one of claims 7, 8, or 9, wherein the TNF α antibody is
15 administered with at least one additional therapeutic agent.

12. A method for inhibiting human TNF α activity in a human subject suffering from a coronary disorder comprising administering a therapeutically effective amount of a TNF α antibody, or an antigen-binding fragment thereof, to the subject, wherein the
20 antibody dissociates from human TNF α with a K_d of 1×10^{-8} M or less and a K_{off} rate constant of $1 \times 10^{-3} \text{ s}^{-1}$ or less, both determined by surface plasmon resonance, and neutralizes human TNF α cytotoxicity in a standard *in vitro* L929 assay with an IC_{50} of 1×10^{-7} M or less.

- 25 13. The method of claim 12, wherein the coronary disorder is restenosis.

14. The method of claim 12, wherein the coronary disorder is selected from the group consisting of acute congestive heart failure, an acute coronary syndrome (including angina and myocardial infarction), arteriosclerosis, chronic arteriosclerosis,
30 cardiomyopathy, congestive heart failure (chronic and acute), and rheumatic heart disease.

15. The method of any one of claims 12, 13, and 14, wherein the TNF α antibody, or antigen-binding fragment thereof, is D2E7.

5 16. A method for inhibiting human TNF α activity in a human subject suffering from restenosis, comprising administering a therapeutically effective amount of a TNF α antibody, or an antigen-binding fragment thereof, to the subject, wherein the antibody dissociates from human TNF α with a K_d of 1×10^{-8} M or less and a K_{off} rate constant of 1×10^{-3} s $^{-1}$ or less, both determined by surface plasmon resonance, and
10 neutralizes human TNF α cytotoxicity in a standard *in vitro* L929 assay with an IC $_{50}$ of 1×10^{-7} M or less.

17. The method of claim 16, wherein the antibody, or antigen binding fragment thereof, is D2E7.

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18. A method of treating or preventing a coronary disorder in a subject comprising administering a therapeutically effective amount of D2E7, or an antigen-binding fragment thereof, to the subject, such that the coronary disorder is treated or prevented.

20 19. The method of claim 18, wherein the coronary disorder is restenosis.

20. The method of claim 18, wherein the coronary disorder is selected from the group consisting of acute congestive heart failure, an acute coronary syndrome (including angina and myocardial infarction), arteriosclerosis, chronic arteriosclerosis,
25 cardiomyopathy, congestive heart failure (chronic and acute), and rheumatic heart disease.

21. A method of treating a subject suffering from restenosis comprising administering a therapeutically effective amount of D2E7, or an antigen-binding
30 fragment thereof, to the subject, such that said restenosis is treated.

23. A method of treating a subject suffering from or at risk of developing restenosis comprising administering a therapeutically effective amount of D2E7, or an antigen-binding fragment thereof, and at least one additional therapeutic agent to the subject, such that the coronary disorder is treated.

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24. The method of claim 23, wherein the additional therapeutic agent is selected from the group consisting of sirolimus, paclitaxel, everolimus, tacrolimus, ABT-578, and acetaminophen.

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25. A kit comprising:

a) a pharmaceutical composition comprising a $\text{TNF}\alpha$ antibody, or an antigen binding portion thereof, and a pharmaceutically acceptable carrier; and

b) instructions for administering to a subject the $\text{TNF}\alpha$ antibody pharmaceutical composition for treating a subject who is suffering from a coronary disorder.

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26. A kit according to claim 23, wherein the $\text{TNF}\alpha$ antibody, or an antigen binding portion thereof, is D2E7.